IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	Group Art Unit: **1646**
Lee *et al.*	Examiner: **John Ulm**
Serial No.: **10/666,689**	Confirmation No: **2217**
Filed: **September 19, 2003**	Customer No: 09157
Title: HUMAN PF4A RECEPTORS (*as amended*)	**Express Mail No. EV384508739 US** **Mail Date: April 14, 2006**

DECLARATION OF JAMES LEE, P.H.D. UNDER 37 C.F.R. § 1.132

Sir:

I, James Lee, Ph.D. declare and say as follows:

1. I am a Principal Research Associate at Genentech, Inc., South San Francisco, CA 94080.

2. I am one of the inventors of the above captioned patent application.

3. I am aware that the claims in the above captioned patent application have been rejected for lacking a specific, substantial and credible utility. I am further aware that the Examiner asserts that the specification does not disclose a specific biological role for the claimed PF4AR polypeptide, or its significance to a particular disease, disorder or biological process which one could manipulate for a desired clinical effect. The Examiner further asserts that Applicants' characterization of the invention is incomplete because they have failed to identify a physiological process which is influenced by the activation or inhibition of the putative PF4A receptor protein. I strongly disagree with the Examiner's conclusion as well as the assertions that Applicants'

characterization of the invention is incomplete and that the utility disclosed is not specific, substantial and credible.

4. I, along with the other inventors of the above captioned patent application, conceived of the PF4AR polypeptides, including the molecule of Figure 5 (SEQ ID NO:6) and variants thereof, as a new member of the platelet factor 4 superfamily. This molecule is now known as CXCR-5. Moreover, we further recognized and disclosed that this molecule would also be a mediator of inflammation. We came to this conclusion based, at least in part, on (a) the shared structural features of the above PF4AR polypeptide to the IL-8R ("CXC" family), specifically (i) the proximity of the N-terminal cysteine residues (*i.e.*, "CXC" v. "CC"); (ii) the shared TM structural components (discussed in the specification at page 15, lines 13-25) and (iii) the use of the IL-8R to isolate the PF4AR polypeptide, and (b) our understanding of the prior art.

5. At the time of the filing of the present invention, the prior art recognized that PF4AR polypeptides, now known as "CXC and CC" chemokines, were mediators of inflammation. For example, the review articles Stoeckle *et al., New Biologist*, 1990, 2(4): 313-323 and Miller *et al., Crit. Rev. Immunol.*, 1992, 12(1,2):17-46 both verify that the state of the art at the time of filing recognized that CXC chemokines played important roles in regulating inflammation. Stoeckle *et al.*, also recognizes that the inhibition of CXC chemokine activity may be an effective anti-inflammatory therapeutic strategy. Stoeckle at 320.

6. The present understanding is that chemokines regulate inflammation because they are the primary regulatory molecules of leukocyte trafficking. This understanding is illustrated in Sabroe *et al., Eur. Respir. J.*, 2002, 19:350-355 and Luster *et al., Nature Immunol.*, 2005, 6(12): 1182-1190. Of particular note is that both of these relatively recent review articles corroborate

Applicants claim that inhibiting leukocyte trafficking, specifically blocking signaling through antagonizing the receptor (*e.g.*, CXCR-5), is an effective therapeutic to treat inflammation. (Sabroe at 350, Luster at 1188).

7. Recently, it was observed by Schmutz *et al., Arthritis Res. Ther.* 2005, 7:R217-R229 that CXCR-5 expression is significantly upregulated in synovial tissue isolated from rheumatoid arthritis patients. The authors further suggest that as a result, CXCR-5 would be a specific therapeutic target in the treatment of the inflammatory disorder rheumatoid arthritis. This disorder is specifically enumerated in the specification on page 14, line 14.

8. Given the evidence set forth in the present declaration, it is my considered scientific opinion that the PF4AR polypeptide CXCR-5 and variants thereof, indeed plays a key role in inflammation, and that this evidence is specific, credible and substantial. In light of the disclosure in the specification, one of ordinary skill would have appreciated and understood the role of CXCR-5 in regulating inflammation as of the filing date. As the understanding of chemokine receptors has developed over time, the connection between inflammation and chemokines in general, as well as CXCR-5 specifically, has been significantly corroborated and verified, as shown above.

9. I hereby declare that all statements made herein are of my own knowledge, are true, and that all statements made on information or belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Signed: _____

James Lee, Ph.D.

Date: April 14, 2006